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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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MCDERMOTT, WILL & EMERY 4370 LA JOLLA VILLAGE DRIVE, SUITE 700 SAN DIEGO, CA 92122				STRZELECKA, TERESA E
ART UNIT		PAPER NUMBER		

1637

DATE MAILED: 02/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/513,362	CHEE ET AL.	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 19 December 2005.
 2a) This action is FINAL. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-38 and 40-43 is/are pending in the application.
 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) 1-38 and 40-43 is/are rejected.
 7) Claim(s) _____ is/are objected to.
 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
 Paper No(s)/Mail Date _____

4) Interview Summary (PTO-413)
 Paper No(s)/Mail Date. _____.
 5) Notice of Informal Patent Application (PTO-152)
 6) Other: _____.

DETAILED ACTION

1. This office action is in response to an amendment filed December 19, 2005. Claims 1-43 were previously pending. Applicants cancelled claim 39. Claims 1-38 and 40-43 are pending and will be examined.
2. Applicants' cancellation of claim 39 obviated the objection to this claim as being non-limiting. Applicants removed double numbers from claims 35, 38 and 43, which obviated the objection to these claims.
3. All other previously presented rejections are maintained for reasons given in the "Response to Arguments" section below.

Response to Arguments

4. Applicant's arguments filed December 19, 2005 have been fully considered but they are not persuasive.

A) Regarding the priority date of the instant claims, Applicants argue that the claims be given priority to all of the claimed provisional applications, since "support for the claimed invention can be found throughout these applications". However, Applicants do not point out exactly where in each of these applications such support is found. Therefore, since the examiner was able to find support for immobilization of enzymes which generate signal from pyrophosphate only in the provisional application No. 60/160,927, filed October 22, 1999 (not 1997, as stated by Applicants), this is the priority date given the instant claims.

B) Regarding the claim interpretation, and specifically the meaning of the term "covalently attached" as applied to multimeric complexes, Applicants seem to be in agreement with the examiner.

C) Regarding the rejection of claims 1-16, 22-27 and 31-42 under 35 U.S.C. 103(a), Applicants main argument centers on the fact that Rothberg et al. seem to be teaching away from using beads in a pyrosequencing method, since they point out to the fact that the beads may be lost during a washing step, citing col. 21, lines 14-34 of Rothberg et al. Applicants further argue that teachings of Rothberg et al. with respect to the minimization of diffusion of pyrophosphate between different nucleic acid templates do not suggest beads as providing such diffusion minimization, and that, “According to Rothberg et al., the combination of pyrophosphate sequencing with microspheres was undesirable, limited and inapplicable to pyrophosphate sequencing strategies”.

However, there are several corrections to be made here. First, the early studies cited by Rothberg et al. were performed with beads suspended in solution, without any support to rest on. Further, the statement “According to Rothberg et al., the combination of pyrophosphate sequencing with microspheres was undesirable, limited and inapplicable to pyrophosphate sequencing strategies” is not a quote from Rothberg et al., but Applicants conclusion. Finally, as to the considerations of PPi diffusion, presented in columns 22-30, it considers an issue of the distance between different immobilized primers and distances between the primers and immobilized enzymes. In order for the PPi molecules to be distinguishable from each other, the primers should be spaced about 50 μ m apart on a planar surface (see, for example, col. 27, lines 7-13). However, as Rothberg et al. point out, different approaches can be used to decrease the distance between the primer immobilization sites (col. 27, lines 42-46). One of the approaches, as described in col. 28, lines 24-32:

“A fifth, and preferred, methodology to allow a decrease in the distance between individual anchor pads, is to conduct the pyrophosphate sequencing reaction in a spatial-geometry which physically-prevents the released PPi from diffusing laterally. For example, uniform cavities, which

are generated by acid-etching the termini of optical fiber bundles, may be utilized to prevent such lateral diffusion of PPi (see Michael, et al., 1998. Randomly Ordered Addressable High-Density Optical Sensor Arrays, *Anal. Chem.* 70: 1242-1248)."

Therefore, as can be seen from the enclosed reference, Rothberg et al. teaches microbead arrays of Walt et al. (see the enclosed reference).

Going back to the argument that Rothberg et al. teaches away from the bead arrays because of the problems with beads being lost during washing, Walt et al. teach the beads being immobilized in the wells of the array (Fig. 6; col. 5, lines 32-36; col. 6, lines 11-16 and 48-67). Therefore, Walt et al., in addition to providing a motivation for using bead arrays in the process of nucleic acid sequencing, provides a solution to the problem of using beads in the process by immobilizing the beads in the wells of the microarray. Thus, one of ordinary skill in the art faced with the teachings of Rothberg et al. and Walt et al. would be motivated to use the bead microarrays of Walt et al. in the pyrosequencing method of Rothberg et al.

The rejection is maintained.

B) Regarding the rejection of claims 18, 19, 28-30 and 43 under 35 U.S.C. 103(a) over Rothberg et al., Walt et al., Nyren et al. and Stratagene Catalog, Applicants reiterate the argument that since Rothberg et al. teach away from using beads, and Nyren et al. and Stratagene Catalog do not provide a motivation for using them, the rejection should be withdrawn. The argument regarding Rothberg et al. reference was addressed above.

The rejection is maintained.

C) Applicants did not argue the rejection of claim 17 under 35 U.S.C. 103(a) over Rothberg et al., Walt et al. and Nyren et al. and rejection of claims 20 and 21 under 35 U.S.C. 103(a) over Rothberg et al., Walt et al., Nyren et al. and Stratagene Catalog, in view of Ross et al.

The rejections are maintained.

Claim Interpretation

5. The term "covalent attachment" has been defined by Applicants on page 27, lines 9-11 in the following way:

"By "covalently attached" herein is meant that two moieties are attached by at least one bond, including sigma bonds, pi bonds and coordination bonds."

However, Applicants also use the term in a broader sense, by describing covalent immobilization of hybridization complexes onto the support, where only one of the elements of the hybridization probe, namely, the capture probe, is covalently attached to the support (page 3, lines 14-16 and 27-30):

"The hybridization complexes comprise the target sequence, the sequencing primer and a capture probe covalently attached to the surface."

"The method comprises providing a hybridization complex comprising the target sequence and a capture probe covalently attached to microspheres on a surface of a substrate and determining the identity of a plurality of bases at the target positions. The hybridization complex comprises the capture probe, an adapter probe, and the target sequence. In one aspect the sequencing primer is the capture probe."

Therefore, the term "covalent attachment" as applied to more than one element is therefore interpreted as meaning that at least one element of the hybridization complex is covalently attached to the support.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

Art Unit: 1637

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. Claims 1-16, 22-27, 31-38 and 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rothberg et al. (U.S. Patent No. 6,274,320 B1; cited in the IDS and in the previous office action) and Walt et al. (U.S. Patent No. 6,327,410 B1; cited in the previous office action).

Claims 1, 10 and 34 will be considered together, since claim 1 is a species of claim 34 and differs from claim 10 by a limitation of sequencing primers covalently attached to the microspheres.

Regarding claims 1, 10 and 34 Rothberg et al. teach a method of sequencing nucleic acids, the method comprising:

a) providing an array comprising:

i) a substrate with a surface comprising discrete sites (Rothberg et al. teach a substrate, which is a fiber optic surfaces, comprising discrete sites (col. 2, lines 66, 67; col. 3, lines 1-6.); and

iii) an enzyme attached at said discrete sites, wherein said enzyme is used to generate a signal from pyrophosphate (Rothberg et al. teach enzymes which generate signal from pyrophosphate attached at discrete sites on the substrate (col. 4, lines 16-28; col. 18, lines 4-8.);

b) providing a first hybridization complex comprising said first domain of a first target sequence and a first sequence primer, wherein said first hybridization complex is attached to said first subpopulation (Rothberg et al. teach providing a first hybridization complex comprising a first domain of a first target sequence and a first sequence primer, where the first hybridization complex is attached to the surface of the support (Fig. 1; col. 3, lines 18-30).);

c) providing second hybridization complex comprising said second domain of a second target sequence and a second sequence primer, wherein said second hybridization complex is attached to said second subpopulation (Rothberg et al. teach providing at least one hybridization complex by providing a plurality of anchor primers and a plurality of nucleic acid templates (= targets) (col. 3, lines 18-30 and 41-45; col. 5, lines 6-15). Rothberg et al. also teach libraries of nucleic acid templates, therefore they inherently teach templates with different sequences (col. 9, lines 25-28; col. 10, lines 32-58).);

d) simultaneously extending said first and second primers by the addition of a first nucleotide to a first detection position using a first enzyme to form first and second extended primers, respectively (Rothberg et al. teach simultaneous addition of a first nucleotide to the first and second hybridization complexes by a polymerase to generate extended primers (col. 3, lines 31-33; col. 14, lines 15-21).);

e) detecting the release of pyrophosphate (PPi) with said enzyme attached at said discrete site within a common reaction chamber of said simultaneous extensions to determine the type of said first nucleotide added onto said first and second primers, respectively (Rothberg et al. teach detection of the pyrophosphate by the enzymes immobilized on the substrate within a common reaction chamber (col. 4, lines 11-28; col. 14, lines 35-41 and 64-66; col. 16, lines 7-14; col. 17, lines 1-9 and 63-67; col. 18, lines 1-8 and 47-67; col. 19, lines 1-8; Fig. 2 and 3; col. 27, lines 58-67; col. 28, lines 1-12 and 60-65).); and

f) determining sequences for said plurality of target nucleic acids (Rothberg et al. teach determining the sequences of the nucleic acids (col. 3, lines 33-40; col. 14, lines 50-56; col. 17, lines 24-36).).

Regarding claim 2, Rothberg et al. teach covalent attachment of anchor primers to the support (col. 7, lines 41, 42) and formation of the hybridization complex on the anchor primer (Fig. 1; col. 3, lines 18-30), therefore they teach covalent attachment of hybridization complexes to the support.

Regarding claim 3, Rothberg et al. teach covalent attachment of anchor primers to the support (col. 7, lines 41, 42) and formation of the hybridization complex on the anchor primer (Fig. 1; col. 3, lines 18-30), therefore they teach attachment of sequencing primers to the support.

Regarding claims 4 and 11, Rothberg et al. teach covalent attachment of anchor primers to the support (col. 7, lines 41, 42) and formation of the hybridization complex on the anchor primer (Fig. 1; col. 3, lines 18-30). Since the anchor primers are capture probes (Fig. 1), Rothberg et al. teach hybridization complexes comprising capture probes and covalent attachment of capture probes to the support.

Regarding claims 5 and 33, Rothberg et al. teach covalent attachment of anchor primers to the support (col. 7, lines 41, 42) and formation of the hybridization complex on the anchor primer (Fig. 1; col. 3, lines 18-30). Since the anchor primers are capture probes which comprise adapter sequences (Fig. 1), Rothberg et al. teach hybridization complexes comprising capture probes and adapter sequences and covalent attachment of hybridization complexes to the support.

Regarding claim 6, Rothberg et al. teach addition of a second nucleotide to the targets using polymerase and detecting the pyrophosphate to determine the second nucleotide (col. 3, lines 37-40; col. 17, lines 24-36).

Regarding claims 7-9, Rothberg et al. teach detecting the PPi by contacting the PPi with ATP sulfurylase (= second enzyme) that converts PPi to ATP and detecting the ATP using a

luciferase (= third enzyme) which generates light, the enzymes being attached to the solid support (col. 4, lines 16-29; col. 14, lines 64-66; col. 16, lines 7-20 and 32-34; col. 18, lines 4-8).

Regarding claims 10 and 12, Rothberg et al. teach covalent immobilization of primers (col. 7, lines 41, 42). Further, since the sequencing primers are a part of the hybridization complex which is covalently attached to the support (Fi. 1), they are covalently attached in that sense as well.

Regarding claim 13, Rothberg et al. teach:

- a) providing a sequencing primer hybridized to said second domain (Rothberg et al. teach providing a sequencing primer which anneals to the target domain (Fig. 1; col. 3, lines 27-30).);
- b) extending said primer by the addition of a first nucleotide to a first detection position using a first enzyme to form an extended primer (Rothberg et al. teach addition of a first nucleotide to the first detection position by a polymerase to generate extended primers (col. 3, lines 31-33; col. 14, lines 15-21).);
- c) detecting the release of pyrophosphate (PPi) to determine the type of said first nucleotide added onto said primer (Rothberg et al. teach detection of the pyrophosphate to determine the type of the nucleotide added to the primer (col. 3, lines 30-37; col. 14, lines 35-41).);
- d) extending said primer by the addition of a second nucleotide to a second detection position using said enzyme (Rothberg et al. teach addition of a second nucleotide to the second detection position (col. 3, lines 30-37; col. 14, lines 13-21).); and
- e) detecting the release of pyrophosphate (PPi) to determine the type of said first nucleotide added onto said primer (Rothberg et al. teach detection of the pyrophosphate to determine the type of the nucleotide added to the primer (col. 3, lines 30-37; col. 14, lines 35-41)).

Regarding claims 14-16, Rothberg et al. teach detecting the PPi by contacting the PPi with ATP sulfurylase (= second enzyme) that converts PPi to ATP and detecting the ATP using a

luciferase (= third enzyme) which generates light, the enzymes being attached to the solid support (col. 4, lines 16-29; col. 14, lines 64-66; col. 16, lines 7-20 and 32-34; col. 18, lines 4-8).

Regarding claims 22-25, Rothberg et al. teach discrete sites on the fiber optic being wells (Fig. 4; col. 6, lines 64-66; col. 7, lines 1-10; col. 20, lines 14-24).

Regarding claim 26, Rothberg et al. teach a substrate comprising a fiber optic bundle (col. 2, lines 66, 67; col. 3, lines 1-6; Fig. 2).

Regarding claim 27, Rothberg et al. teach glass and plastic supports (col. 2, lines 18-20; col. 19, line 41).

Regarding claims 34, 37 and 42, Rothberg et al. teach genomic DNA (col. 34-38).

Regarding claims 35 and 38, Rothberg et al. teach enzymes attached to the substrate (col. 4, lines 26-28).

Regarding claims 36 and 41, Rothberg et al. teach PCR products as targets (col. 11, lines 9-30).

Regarding claim 40, Rothberg et al. teach target sequences covalently attached to the substrate (col. 14, lines 12-15; col. 7, lines 41, 42).

B) Rothberg et al. teach attachment of reactants to the surface of the fiber optic, but do not teach microspheres on the surface of the fiber optic bundle.

C) Regarding claims 1, 10 and 34, Walt et al. teach microsphere-based analytical chemistry system in which the microspheres are distributed on a fiber optic bundle (Abstract). The surface of the substrate comprises discrete sites into which at least two subpopulations of microspheres are distributed. Each of the microspheres comprises a bioactive agent and an optical signature which allows identification of the bioactive agent. The beads are randomly distributed on the array (col. 3, lines 35-45; col. 4, lines 54-56). The bioactive agent attached to the microsphere is a nucleic acid,

particularly a nucleic acid probe (col. 7, lines 55-66; col. 8, lines 15-19; col. 9, lines 41-67; col. 10, lines 1-47). The array is used for sequencing (col. 24, lines 51-52).

Regarding claims 22-25, Walt et al. teach substrate with discrete sites, first and second populations of the microspheres (col. 3, lines 35-40), the discrete sites being wells (Fig. 5; col. 6, lines 22-24) and microspheres randomly distributed in these sites (col. 4, lines 54-56). Walt et al. teach the substrate being a fiber optic bundle (col. 6, lines 32-35).

Regarding claim 31, Walt et al. teach decoding of the array prior to the testing performed on the array (col. 4, lines 56-58; col. 22, lines 19-25).

Regarding claim 32, Walt et al. teach the microspheres containing a probe (=identifier binding ligand) which binds a decoder binding ligand (= target nucleic acid) (col. 10, lines 43-47; col. 21, lines 17-60). Since each of the beads contains a unique optical signature (col. 13, lines 8-24), the identity and location of each bead can be determined.

Regarding claims 35 and 38, Walt et al. teach enzymes immobilized on microspheres (col. 20, lines 51-67; col. 25, lines 57-67; col. 26, lines 1-25).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the microspheres of Walt et al. distributed over the surface of the fiber optic sensor in the method of nucleic acid sequencing of Rothberg et al. The motivation to do so, provided by Walt et al., would have been that (col. 3, lines 13-26):

“The innovation of the two previous patents was the placement of multiple chemical functionalities at the end of a single optical fiber bundle sensor. This configuration yielded an analytic chemistry sensor that could be remotely monitored via the typically small bundle. The drawback, however, was the difficulty in applying the various chemistries associated with the chemical functionalities at the sensor's end; the functionalities were built on the sensor's end in a

serial fashion. This was a slow process, and in practice, only tens of functionalities could be applied. Accordingly, compositions and methods are desirable that allow the generation of large fiber optic arrays including microspheres that can be either encoded or decoded to allow the detection of target analytes.” and (col. 4, lines 35-56):

“The present invention is based on two synergistic inventions: 1) the development of a bead-based analytic chemistry system in which beads, also termed microspheres, carrying different chemical functionalities may be mixed together while the ability is retained to identify the functionality of each bead using an optically interrogatable encoding scheme (an “optical signature”); and 2) the use of a substrate comprising a patterned surface containing individual sites that can bind or associate individual beads. This allows the synthesis of the bioactive agents (i.e. compounds such as nucleic acids and antibodies) to be separated from their placement on an array, i.e. the bioactive agents may be synthesized on the beads, and then the beads are randomly distributed on a patterned surface. Since the beads are first coded with an optical signature, this means that the array can later be “decoded”, i.e. after the array is made, a correlation of the location of an individual site on the array with the bead or bioactive agent at that particular site can be made. This means that the beads may be randomly distributed on the array, a fast and inexpensive process as compared to either the *in situ* synthesis or spotting techniques of the prior art.”

8. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rothberg et al. (U.S. Patent No. 6,274,320 B1; cited in the IDS and in the previous office action) and Walt et al. (U.S. Patent No. 6,327,410 B1; cited in the previous office action), as applied to claim 10 above, and further in view of Nyren et al. (WO 98/13523; cited in the previous office action).

A) Rothberg et al. teach pyrosequencing using nucleotides, but do not teach protected nucleotides.

B) Nyren et al. teach pyrosequencing (Abstract) using 3'protected nucleotides (page 17, third paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the 3'-protected nucleotides of Nyren et al. in the method of pyrosequencing of Rothberg et al. and Walt et al. The motivation to do so, provided by Nyren et al., would have been that using protected nucleotides allowed chain extension to proceed one position at a time without complications caused by sequences of identical bases (page 17, third paragraph).

9. Claims 18, 19, 28-30 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rothberg et al. (U.S. Patent No. 6,274,320 B1; cited in the IDS and in the previous office action), Walt et al. (U.S. Patent No. 6,327,410 B1; cited in the previous office action), Nyren et al. (WO 98/13523; cited in the previous office action) and Stratagene Catalog (1988, p. 39; cited in the previous office action).

A) Regarding claim 18, Rothberg et al. teach a kit comprising:

a) composition comprising:

i) a substrate with a surface comprising discrete sites (Rothberg et al. teach a surface of a substrate comprising discrete sites, for example, pads with attached anchor primers or wells (col. 2, lines 66, 67; col. 3, lines 1-6; col. 6, lines 64-67; col. 7, lines 1-15; col. 20, lines 15-18).);

ii) a population of microspheres distributed on said sites, wherein said microspheres comprise different capture probes, wherein said array is configured for simultaneous contact of said different capture probes with a common reaction chamber (Rothberg et al. teach a substrate with a plurality of anchor primers (=capture probes) (Fig. 1; col. 3, lines 19-24 and 42-45). Rothberg et al. teach simultaneous contact of different

capture probes in a common reaction chamber (col. 17, lines 63-67; col. 18, lines 1-3 and 40-67; Fig. 2.); and

iii) an enzyme attached at said discrete sites wherein said enzyme is used to generate a signal from pyrophosphate (Rothberg et al. teach enzymes ATP sulfurylase and luciferase immobilized on solid support and generation of signal from pyrophosphate using these enzymes (col. 3, lines 11-22; col. 18, lines 4-8).);

b) a first extension enzyme (Rothberg et al. teach extension of the sequencing primer with a polymerase (= first enzyme) (col. 3, lines 30-33; col. 22, lines 45-55).); and

c) dNTPS (Rothberg et al. teach dNTPs (col. 17, lines 24-30).).

Regarding claim 19, Rothberg et al. teach detection of pyrophosphate using ATP sulfurylase (= second enzyme) (col. 14, lines 64-66) and detection of ATP using luciferase (= third enzyme) (col. 16, lines 7-20 and 33-35), with the enzymes attached to solid support (col. 3, lines 11-22; col. 18, lines 4-8).

Regarding claim 28, Rothberg et al. teach wells on the surface of the fiber optic bundle (Fig. 4; col. 6, lines 64-66; col. 7, lines 1-10; col. 20, lines 14-24).

Regarding claim 29, Rothberg et al. teach a substrate comprising a fiber optic bundle (col. 2, lines 66, 67; col. 3, lines 1-6; Fig. 2).

Regarding claim 30, Rothberg et al. teach glass and plastic supports (col. 2, lines 18-20; col. 19, line 41).

Regarding claim 43, Rothberg et al. teach enzymes attached to the substrate (col. 4, lines 26-28).

B) Rothberg et al. teach attachment of reactants to the surface of the fiber optic, but do not teach microspheres on the surface of the fiber optic bundle.

C) Regarding claim 18, Walt et al. teach microsphere-based analytical chemistry system in which the microspheres are distributed on a fiber optic bundle (Abstract). The surface of the substrate comprises discrete sites into which at least two subpopulations of microspheres are distributed. Each of the microspheres comprises a bioactive agent and an optical signature which allows identification of the bioactive agent. The beads are randomly distributed on the array (col. 3, lines 35-45; col. 4, lines 54-56). The bioactive agent attached to the microsphere is a nucleic acid, particularly a nucleic acid probe (col. 7, lines 55-66; col. 8, lines 15-19; col. 9, lines 41-67; col. 10, lines 1-47). The array is used for sequencing (col. 24, lines 51-52).

Regarding claim 43, Walt et al. teach enzymes immobilized on microspheres (col. 20, lines 51-67; col. 25, lines 57-67; col. 26, lines 1-25).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the microspheres of Walt et al. distributed over the surface of the fiber optic sensor in the method of nucleic acid sequencing of Rothberg et al. The motivation to do so, provided by Walt et al., would have been that (col. 3, lines 13-26):

“The innovation of the two previous patents was the placement of multiple chemical functionalities at the end of a single optical fiber bundle sensor. This configuration yielded an analytic chemistry sensor that could be remotely monitored via the typically small bundle. The drawback, however, was the difficulty in applying the various chemistries associated with the chemical functionalities at the sensor's end; the functionalities were built on the sensor's end in a serial fashion. This was a slow process, and in practice, only tens of functionalities could be applied. Accordingly, compositions and methods are desirable that allow the generation of large fiber optic arrays including microspheres that can be either encoded or decoded to allow the detection of target analytes.” and (col. 4, lines 35-56):

"The present invention is based on two synergistic inventions: 1) the development of a bead-based analytic chemistry system in which beads, also termed microspheres, carrying different chemical functionalities may be mixed together while the ability is retained to identify the functionality of each bead using an optically interrogatable encoding scheme (an "optical signature"); and 2) the use of a substrate comprising a patterned surface containing individual sites that can bind or associate individual beads. This allows the synthesis of the bioactive agents (i.e. compounds such as nucleic acids and antibodies) to be separated from their placement on an array, i.e. the bioactive agents may be synthesized on the beads, and then the beads are randomly distributed on a patterned surface. Since the beads are first coded with an optical signature, this means that the array can later be "decoded", i.e. after the array is made, a correlation of the location of an individual site on the array with the bead or bioactive agent at that particular site can be made. This means that the beads may be randomly distributed on the array, a fast and inexpensive process as compared to either the *in situ* synthesis or spotting techniques of the prior art."

D) Neither Rothberg et al. nor Walt et al. teach kits.

E) Nyren et al. teach a kit for sequencing of DNA by pyrophosphate release, the kit comprising a sequencing primer, a polymerase, a detection enzyme means for identifying pyrophosphate release, dNTPs or ddNTPs (page 20, second paragraph; page 21, first paragraph).

F) Stratagene catalog teaches a motivation to combine reagents into kit format (page 39).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the method of Rothberg et al. and Walt et al. into a kit format as discussed by Stratagene catalog and suggested by Nyren et al., since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of

experiments. Thus one need not purchase gram quantitites of 10 different reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantitites you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control" (page 39, column 1).

10. Claims 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rothberg et al. (U.S. Patent No. 6,274,320 B1; cited in the IDS cited in the previous office action), Walt et al. (U.S. Patent No. 6,327,410 B1; cited in the previous office action), Nyren et al. (WO 98/13523; cited in the previous office action) and Stratagene Catalog (1988, p. 39; cited in the previous office action), as applied to claim 18 above, and further in view of Ross et al. (WO 91/06678; cited in the previous office action).

A) Teachings of Rothberg et al., Walt et al., Nyren et al. and Stratagene Catalog are presented above. None of these references teaches labeled nucleotides or different labels on nucleotides.

B) Ross et al. teach sequencing of nucleic acids by sequential addition of 3'-blocked nucleotides to the template (Abstract; page 11, lines 28-36; page 12; page 13, lines 1-29). The different types of nucleotides are labeled with different labels (page 12, lines 14-18).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used labeled nucleotides of Ross et al. in the sequencing kit of Rothberg et al., Walt et al., Nyren et al. and Stratagene Catalog. The motivation to do so, provided by Ross et al.,

would have been that incorporation of nucleotides was monitored by detecting the label on the dNTP (page 26, lines 1-5) and using fluorescent labels increased detection sensitivity (page 31, lines 1-5).

11. No claims are allowed.

Conclusion

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E. Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

TERESA STRZELECKA
PATENT EXAMINER
Teresa Strzelecka
2/17/06